REVIEW

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ENDOMETRIOSIS IN ADOLESCENTS

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Abstract. *Endometriosis is an estrogen-dependent chronic inflammatory disease characterized by the proliferation of endometrial glandular tissue and stroma outside the uterine cavity. It is estimated that 4 to 17% of adolescent girls have the same form of endometriosis, and it is particularly common among those with dysmenorrhea who respond poorly to analgesics or estroprogestins. For those suffering from recurrent and chronic pelvic pain, the percentage rises to 25-38%. Possible explanations for the pathogenesis of endometriosis are: coelomic metaplasia, embryonic Müllerian rests, iatrogenic implantation, vascular and lymphatic metastasis, the genetic theory, and endometrial stem/progenitor cells that represent different hypotheses besides Sampson's theory, the classic retrograde menstruation, which is the most widely accepted theory to explain the ectopic implantation of endometrium. According to the ESHRE guidelines, suggestive manifestations for endometriosis include early menarche, severe dysmenorrhea, dyspareunia, abnormal uterine bleeding, midcycle or acyclic pain, resistance to empiric medical treatment, and gastrointestinal and genitourinary symptoms. Known risk factors for developing endometriosis include: genetic predisposition; epigenetic variables – prematurity, bottle feeding, exposure to some pollutants with estrogenic activity; dysregulation of the immune and inflammatory response, as well as obstructive anomalies of the reproductive tract. Diagnosis is made by accurate anamnesis – personal and family history, gynecological examination and ultrasonographic evaluation (transabdominal and transvaginal ultrasound). Magnetic resonance can be useful to detect obstructive reproductive tract anomalies and to identify and characterize endometriotic lesions that are difficult to locate by ultrasound. A multidisciplinary diagnostic approach should be considered for a complete evaluation of these patients. Laparoscopic evidence serves as the gold standard for verifying peritoneal endometriosis and determining its stage, spread, and severity. A differential diagnosis of gastrointestinal pathologies, Müllerian anomalies, recurrent infections, and adenomyosis must be made. The treatment of this disease includes medical and surgical interventions, and a combination of both. ESRHE guidelines advise clinicians treating women with endometriosis to prescribe hormonal contraceptives or progestins to reduce endometriosis-associated pain. The use of gonadotropin hormone-releasing hormone agonists is acceptable in adolescents only if the patient with known endometriosis is refractory to other medical therapies or surgical treatments. The goals of medical therapy in the adolescent patient include symptomatic relief, suppression of disease progression, and protection of future fertility.*

Key words: *endometriosis, adolescents, therapeutic management*

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INTRODUCTION

Endometriosis is an estrogen-dependent chronic inflammatory disease characterized by the proliferation of endometrial glandular tissue and stroma outside the uterine cavity. According to the American Endometriosis Association, 60% of women diagnosed with pelvic endometriosis report onset of symptoms before the age of 20 years [1].

The first evidence of this disease dates back to the 19th century, when Rokitansky expressed an opinion that endometrial glands and stroma could be found in ovarian and uterine tumors. He was the first to describe adenomyosis, calling it an "adenomatous polyp". Cullen was the first to describe peritoneal endometriosis, calling it "adenomyoma". In 1899, Russell published evidence of uterine mucosa covering the ovary, but Sampson was the first to demonstrate endometrial cycle-specific changes in ectopic endometriotic foci [2].

According to the World Health Organization (WHO), endometriosis is diagnosed in 10% of all women of reproductive age (176 million women worldwide). It is estimated that 4 to 17% of adolescent girls have some form of endometriosis, and it is higher among those with dysmenorrhea who respond poorly to or are unaffected by analgesic or estroprogestin therapy. For those suffering from recurrent and chronic pelvic pain, the percentage reaches 25-38% [1, 3].

There are a number of theories attempting to explain the pathogenesis of this disease, the most common being Sampson's theory, according to which endometriosis is the result of retrograde menstruation and implantation of viable endometrial cells in the peritoneal cavity. However, this theory cannot explain the occurrence of endometriosis in girls before menarche. It is necessary to take into consideration coelomic metaplasia or the appearance of endometriotic foci from Müllerian rests, which are transformed by endogenous steroid hormones. According to other publications, the early manifestation of the disease may be associated with neonatal uterine bleeding, which occurs in 3-5% of newborns between 3-5 days of birth. The length of the cervix and the dense cervical mucus lead to functional obstruction, with subsequent retrograde bleeding, during which viable progenitor cells are shed into the peritoneal cavity. Halban's theory explains the presence of distant localizations of endometriotic foci by metastatic spread of endometrial cells via the blood and lymphatic vessels. There are also iatrogenic, genetic theories, as well as impaired immune and inflammatory responses in patients affected by this disease and despite the numerous theories, the pathogenesis is still not fully understood [1, 4, 5].

RISK FACTORS

Genetic predisposition is present in 50% of cases, with common variants found in 26%. It is known that in an affected first-degree relative, the risk of developing the disease increases by seven to ten times relative to the general population, which is likely due to polygenic and multifactorial inheritance [6].

Obstructive Müllerian anomalies are another risk factor. In these cases, the amount of retrograde menstruation increases, and the likelihood of implantation of viable endometrial cells increases [7]. Early age of menarche – before 12 years of age and short menstrual cycles are another risk factor [8]. The influence of certain pollutants and foods with estrogenic influence, prematurity and low birth weight, and passive smoking is discussed. Impaired immune and inflammatory responses, in turn, try to explain

the manifestation of this disease in patients with a higher incidence of concomitant autoimmune diseases, bronchial asthma, migraine and polyallergies. Patients with endometriosis have been found to have higher levels of cytokines, chemokines, and growth factors, as well as decreased NK cell activity [1].

CLINICAL PICTURE

The clinical picture is dominated by pelvic pain, which can be cyclical but is much more often acyclic. A number of concomitant symptoms have been reported on the gastrointestinal side, such as constipation, tenesmus, presence of blood in stools, dyschezia and irritable bowel syndrome, and on the urinary side, dysuria, haematuria, and nocturia. Nausea, vomiting and severe headache are also seen in a large proportion of cases [5].

CLINICAL EVALUATION

The clinical evaluation of patients with endometriosis in adolescence does not differ significantly from that of patients of reproductive age. An accurate anamnesis is of utmost importance. The questions focus on the characteristics of the pain and its relationship to the menstrual cycle. The VAS (Fig. 1), where patients report pain greater than 7 points, and screening questionnaires that patients complete are handy. Attention is paid to the age of menarche, duration of menstrual cycles and family history. It is important to assess how the pain syndrome affects daily activities such as days off school, physical activity, sleep quality and sexual activity [1, 5, 9].

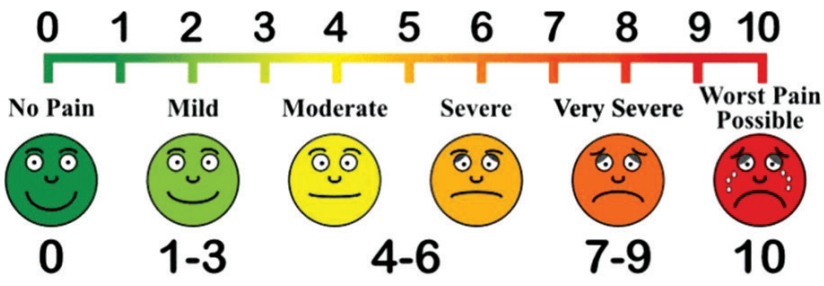

Fig. 1. Visual Analog Scale with Wong-Baker facial ideographic scale

The gynecological examination is primarily aimed at excluding other nosological entities that may lead to the manifestation of chronic pelvic pain. In sexually active patients, bimanual palpation may reveal a retroverted uterus with limited mobility. Patients report tenderness on palpation of the fornix and the rectovaginal space. Rectal examination may reveal compacted and nodularly altered sacro-uterine ligaments [10]. Paraclinical examinations come to aid the differential diagnostic process. Test to avoid – Ca 125 is most commonly used as a biomarker for ovarian cancer, but can be elevated in a number of other conditions, as well as endometriosis. CA 125 is not a useful test for screening and diagnosis due to its low sensitivity and specificity [11].

IMAGING METHOD

Transabdominal ultrasonography visualizes ovarian endometriosis but is an inferior method for diagnosing superficial pelvic endometriosis, which is the most common form in adolescent patients. The transvaginal approach allows evaluation of the uterine body, visualization of heteroechogenic islands in the myometrium or avascular cystic areas when adenomyosis is suspected.

Ovarian endometriosis, according to the IOTA classification, is most often represented by unilateral hypoechogenic “frosted glass” type cysts with weak vascularization. In 25% of cases, they may have an atypical appearance – multilocular formations with avascular papillary growths, hyperechogenic foci due to calcifications, and solid areas. They may be represented by solid and liquid components [1, 10]. Because foci in superficial pelvic endometriosis are difficult to visualize by ultrasonography, so-called “soft markers” are used, i.e., reduced mobility of the ovary and/or uterine body, as well as of the rectum relative to the uterine body [12].

Magnetic resonance imaging (MRI) can be useful for diagnosing obstructive anomalies of the reproductive tract and for identifying endometriotic lesions that are difficult to localize by ultrasound, but, due to its high cost, it cannot be used as a screening method [13].

The diagnosis is often made during laparoscopic surgery, which remains the „gold standard“. The use of diagnostic laparoscopy is indicated in cases of persistent pain syndrome for more than three months or in cases of poor or no response to nonsteroidal anti-inflammatory drugs and/or hormonal therapy. The laparoscopic findings in adolescent endometriosis are mainly represented by atypical changes, i.e., clear, red or white lesions or small peritoneal defects, which are subject to pathohistological verification [1, 14].

A wide palette of diseases affecting the gastrointestinal tract, urinary system, skeletal-muscular diseases and neurological diseases comes into consideration

in the differential diagnostic plan. On the side of the reproductive system, the following should be excluded: adenomyosis, postoperative adhesive syndrome, pelvic inflammatory disease, ovarian formations, obstructive anomalies of the genital tract, vulvodynia, and hydrosalpinx. The evaluation of patients should be performed by a multidisciplinary team because of the multiple nosological entities that may be involved in the presentation of chronic pelvic pain [5].

Endometriosis is a chronic disease with an unpredictable course. The majority of studies have shown the evolution of minimal lesions in adolescents into classic forms in adults in the absence of timely therapy. Therefore, prolonged medical treatment is of utmost importance to control pain and stop disease progression. Prolonged medical treatment is indicated even after complete surgical removal of endometriotic lesions because of the high recurrence rate (10-55%) in the absence of such treatment.

Similar to endometriosis in adults, endometriosis in adolescent patients is considered to be an inflammation-mediated estrogen-dependent disease [15]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are indicated as first-line treatment for pain syndrome, with dosage based on body weight and intake starting depending on the timing of symptoms. Fluid intake is increased during NSAID administration for nephroprotection. Ibuprofen is a widely available and affordable NSAID with good tolerability. It reaches peak plasma concentration in 40 min and has a plasma half-life of 2-4 hours. A characteristic of the drug is that it does not increase menstrual blood loss, which is the effect of Ketoprofen and Naproxen [1]. COX inhibitors (COX are enzymes key to the production of inflammatory mediators) may come into consideration in pain control, and although both COX1 and COX2 receptors are present in ectopic endometriotic foci, studies have shown that COX2 receptors are present at higher concentrations. Along with pain control, new studies suggest that selective COX2 inhibitors may also inhibit endometrial tissue proliferation, induce apoptosis, and suppress neoangiogenesis [16].

THERAPY

Combined oral contraceptives (COCs) or gestagens alone are the first-line hormonal medications used in the therapeutic plan of patients with endometriosis. The therapeutic effect of COCs is mediated by suppression of the hypothalamic-pituitary-ovarian axis (HPO) activity, reducing menstrual blood loss and, in particular, retrograde menstruation as well as the peritoneal inflammatory response. Their administration induces endometrial hypotrophy, suppresses COX-2 and prostaglandin synthesis, and reduces acyclic and ovulatory pain. As a positive effect of their long-term use should be mentioned a reduced risk of neoplastic processes of the ovary, since it is known that in patients with endometriosis, there is an increased risk for endometrioid and clear cell ovarian carcinomas. The use of combined oral contraceptives should be individualized and the presence of contraindications. Compared with cyclical administration, continuous therapy with COCs has been shown to have better pain control. If no relief of symptoms is observed after four months of hormonal therapy, surgical treatment comes into consideration. In 11 to 19% of patients, the pain syndrome is not affected by empiric therapy [5].

The administration of gestagens as a stand-alone therapy has an antigonadotropic effect, leading to anovulation and suppression of ovarian steroidogenesis, as well as to decidualization and atrophy of ectopic foci. They modulate the immune response by suppressing the synthesis of inflammatory mediators (PGs, ILs) and growth factors (NGFs, VGFs). Norethisterone acetate (NETA) at a dose of 2.5-5 mg/day is recommended for use in adolescence. It has a long half-life (40-50 hours) and is partially metabolized to ethinyl estradiol. At a dose of 5 mg/day, it suppresses the preovulatory LH peak. Its prolonged use results in secondary amenorrhea with the possibility of breakthrough bleeding. New-onset acne has been reported as a side effect. Its influence on plasma lipids and bone mineral density is negligible. Another gestagen with widespread use is Dienogest (DNG) at a dose of 2 mg/day. Its prolonged administration leads to endometrial hypotrophy through direct receptor interference and the suppression of neoangiogenesis and the synthesis of inflammatory mediators. DNG promotes apoptosis in ectopic foci. Its half-life is 10 hours, and it is well tolerated. As side effects have been reported – spotting, secondary amenorrhea, chest tightness, headache. Less frequently, changes in body weight and in mood may be observed. It also affects lipid profile and bone mineral density. These side effects tend to diminish after the first six months of use. Normal menstrual cycles are usually restored within two months after discontinuation of DNG therapy.

Levonorgestrel-releasing intrauterine devices (LNG-IUS) contain 50 mg of levonorgestrel, with 20 micrograms of the hormone released in 24 hours over 5 years. Better compliance has been reported by avoiding oral administration and daily commitment. Effects of LNG-IUDs are endometrial atrophy, hypomenorrhea with reduction in retrograde menstruation and higher progesterone concentration in the

peritoneal cavity, suppressing ectopic foci activity. The effect in terms of pain syndrome is commensurate with that of the use of GnRH agonists. A lower recurrence rate after discontinuation of therapy has also been reported. LNG-IUDs are not appropriate as first-line hormonal therapy in patients in the first years after menarche and in those who do not have a sexual life. Appropriate LNG-IUDs may be placed in the course of laparoscopic surgical removal of endometriotic foci, with the goal of continued hormonal therapy to prevent subsequent recurrences [1, 5, 17].

The second line of hormone therapy is the group of GnRH agonists. Their successful use is based on the fact that they lead to hypoestrogenism by blocking ovarian steroidogenesis, which accelerates the regression of ectopic endometriotic implants. During the first few days of administration, GnRH agonists stimulate the release of LH and FSH from the pituitary, but chronic administration results in suppression of the hypothalamic-pituitary-ovarian axis. The result is hypoestrogenism, secondary amenorrhea, and regression of endometriotic implants by depriving the implants of estrogen. GnRH agonists are available in both injectable and nasal forms for administration. Of these, in adolescence, Leoprolide/ Triptorelin 3.75 mg once monthly or 11.25 mg used once every three months can be administered. They are approved for use only up to 6 months because of the known side effects of hypoestrogenism – bone mass loss, vaginal atrophy and dryness, hot flashes and abnormalities in lipid profile. Add-back therapy (ABT) provides symptomatic relief and reduces the rate of bone loss. ABT in this age group is composed of 1 mg of estradiol (Ethinyl estradiol, estradiol valerate) and gestagen (NETA 5mg/Dydrogesterone 10 mg). Concomitantly with ABT, the intake of Vit. D and calcium should be increased, and bone mineral density should be monitored. The use of GnRH agonists in adolescence comes into consideration only in cases of a histologically proven diagnosis, persistent pain syndrome after surgical treatment, unrelieved by empirical therapy or in the treatment of endometriosis with atypical localization – pleural, intracranial, pericardial, etc. [1, 18].

Compared to GnRH agonists, GnRH antagonists do not cause an initial flare-up of symptoms and their administration results in less pronounced hypoestrogenism. This group of medications has a better side effect profile. Elagolix is an oral GnRH receptor antagonist that inhibits endogenous GnRH signaling by competitively binding to GnRH receptors in the pituitary gland. It was approved for use by the FDA in July 2018 for the treatment of moderate to severe pain associated with endometriosis. Its administration results in dose-dependent suppression of LH and FSH release, resulting in hypoestrogenism. Elagolix and Linzagolix are part of the therapeutic plan in patients of reproductive age, but there are currently insufficient studies and data on their use in adolescent patients [19].

Aromatase inhibitors are used to treat patients with endometriosis at reproductive age. Aromatase P450 is the key enzyme for estrogen biosynthesis in the ovary. It catalyzes the conversion of androstenedione and testosterone synthesized in ovarian theca cells to estrone and estradiol (E2) in granulosa cells. There is abundant evidence showing that endometriotic lesions express aromatase and are able to synthesize their own estrogens. In view of this observation, the use of a third-generation aromatase inhibitor, Letrozole (AI), to treat endometriosis is an attractive concept. There are insufficient data on the use of this group of medications in adolescence. Still, they are known to be used in patients with precocious puberty, short stature, and girls with McCune-Albright syndrome [20, 21].

Surgical treatment in patients with endometriosis in adolescence comes into consideration in cases with increasing size of ovarian endometriosis or persistence of the pain syndrome despite hormonal therapy, as well as in cases when ovarian neoplasia cannot be excluded by imaging methods of diagnosis. The goal of surgical treatment should be the complete removal of visible lesions and restoration of the patient's normal anatomy. In adolescent patients, surgical interventions should be as sparing as possible. Radical excision of superficial endometriosis is not practiced because of the risk of extensive adhesive postoperative complications. Compared with patients of reproductive age, those in adolescence have been reported to have a higher recurrence rate over a 5-year period, with a 40-50% recurrence rate in adolescents without subsequent surgical treatment with hormone therapy [5].

CONCLUSION

Endometriosis is an estrogen-dependent chronic inflammatory disease with a progressive course that affects all aspects of a girl's life. The therapeutic approach to patients with adolescent endometriosis should be individualized, and cases should be evaluated by a multidisciplinary team. The aim is to shorten the time from symptom onset to diagnosis and the initiation of timely treatment. The goals of medical therapy in adolescent patients include symptom

relief, slowing disease progression, and protecting future fertility.

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